

# **An audit of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics**

Slindokuhle Sibiya

Student Number: 2307784

Supervisor: Ms. Monica Araujo

Co-supervisor: Mrs. Elzette Gilfillan



A research report (in the format of a “submissible” paper) submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine (Genetic Counselling)

Johannesburg, 2017

# NATIONAL HEALTH LABORATORY SERVICE

School of Pathology, University of the Witwatersrand



## DIVISION OF HUMAN GENETICS



Hospital Street, Johannesburg, 2001 | PO Box 1038, Johannesburg, 2000

[T] +27 11 489 9223 | [M] +27 78 080 8841 | [F] +27 11 489 9226 | [E] human.genetics@nhls.ac.za

20 January 2025

Dear Examiner,

**Re: Research report submitted to the Faculty of Health Sciences by Ms Slindokuhle Sibiya in partial fulfilment of the requirements for the degree of Master of Science in Medicine (Genetic Counselling)**

Thank you for agreeing to review the research report titled, "An audit of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics."

The candidate, Ms. Slindokuhle Sibiya, has submitted her research report in the form of a "submissible" paper, which accounts for 30% of the final grade for her degree. The candidate and her supervisors have selected the South African Medical Journal for submission. Accordingly, the attached manuscript has been prepared following the journal's author guidelines, which are also included for your reference. The only adjustment made for your review is that the manuscript is presented as a single document (including tables and figures) to facilitate marking, rather than as separate components.

Additionally, the research protocol is included as an appendix to provide an extended literature review and further context for the study. Please note that the protocol has already been reviewed and approved by the Faculty of Health Sciences and is not part of this examination. For a full overview of the materials included in this submission, please refer to the Table of Contents.

Yours Sincerely,

Student: Slindokuhle Sibiya

Supervisor: Monica Araujo

Co-supervisor: Elzette Gilfillan

This report is intended solely to record the observations and/or opinion of the writer. It does not constitute a medico-legal report

Chairperson: Prof Eric Buch CEO: Dr Karmani Chetty  
Physical Address: 1 Modderfontein Road, Sandringham, Johannesburg, South Africa Postal Address: Private Bag X8, Sandringham, 2131, South Africa  
Tel: +27 (0) 11 386 6000/ 0860 00 NHLS(6457) www.nhls.ac.za  
Practice number: 5200296

## Declaration

I, Slindokuhle Sibiya, declare that this research report (in the format of a “submissible” paper) is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine (Genetic Counselling) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



*Slindokuhle Sibiya*

*Student Number: 2307784*

20<sup>th</sup> day of June 2025 in Johannesburg

## Contribution of Candidate

### Student's contribution to the article(s) and agreement of co-author(s)

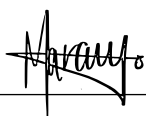
I, Slindokuhle Sibiya, student number 2307784, declare that this Research Report, entitled “An audit of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics”, is my own work and that I contributed significantly towards the research findings presented in the paper intended for publication below.



Signature of student

20/06/2025

Date

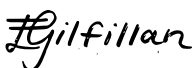
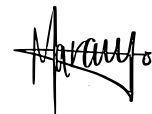


Signature of Primary Supervisor

20.06.2025

Date

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the research findings intended for a published article by the student as part of their Research Report.

| Authors         | Name                  | Signature                                                                            | Date                       |
|-----------------|-----------------------|--------------------------------------------------------------------------------------|----------------------------|
| 1 <sup>st</sup> | Ms Slindokuhle Sibiya |   | 20 <sup>th</sup> June 2025 |
| 2 <sup>nd</sup> | Mrs Elzette Gilfillan |  | 20.06.2025                 |
| 3 <sup>rd</sup> | Ms Monica Araujo      |  | 20.06.2025                 |

## **Presentations arising from this research project**

1. Genetic Counsellors South Africa Research Showcase 2024, 21<sup>st</sup> November, (oral presentation)

## **Abstract**

Breast cancer remains a leading cause of cancer-related deaths globally, with incidence rates steadily rising in South Africa over the past two decades. Despite efforts such as screening programs and predictive testing, early detection and treatment are hindered by delayed diagnoses, limited healthcare access, and socioeconomic challenges, particularly in low- to middle-income countries. Micro-level assessments, such as clinical audits, are essential to identify gaps and improve care strategies. This study aimed to construct a patient profile of genetic testing outcomes and sociodemographic factors for individuals who underwent genetic counselling for hereditary breast cancer over six years (September 2018–January 2024) at the National Health Laboratory Services (NHLS), Braamfontein. Data from 619 patient files were extracted from the departmental REDCap database. Extracted variables included demographic, personal, family, and medical history, alongside genetic testing uptake and outcomes. Statistical analyses included descriptive statistics, Chi-squared tests, t-tests, ANOVA, and multiple regression modelling. The study included 619 participants, with 594 (95.96%) eligible for diagnostic testing and 25 (4.04%) eligible for predictive testing. Diagnostic testing participants were predominantly of Black ancestry, state-sector patients, and urban residents, while predictive testing participants were mainly White, private-sector patients. Diagnostic testing uptake was 78.96%. Sociodemographic factors influenced testing uptake and outcomes; younger age and employment increased acceptance, while Black ancestry and older age were linked to fewer actionable results. While predictive testing uptake was 88.00%, the number of proband relatives presenting for predictive testing relative to those eligible was notably low. Findings suggest targeted education and research can improve awareness and genetic testing, addressing South Africa's breast cancer burden.

## **Acknowledgements**

Firstly, praise be to God – my source of strength and refuge – who has carried me through this year and this project. *“The Lord is my strength and my shield; my heart trusts in Him, and He helps me.”*

Thank you to all my sponsors who have given me the opportunity to study and have seen potential in me, entrusting me with their support. I hold you in my heart, as none of this would have been possible without you.

A special thank you to the patients who consented to the use of their data in research. Your trust allows us to foster improvements in the field – you are the true heroes.

To my supervisors – Monica and Elzette, fellow classmates, and the genetic counselling interns: thank you for your guidance, knowledge, and support throughout this journey.

Finally, to my family and friends, even though you didn’t always fully understand, you offered a listening ear and a shoulder to cry on – for that, I am deeply grateful.

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### **List of Abbreviations**

|                    |                                       |
|--------------------|---------------------------------------|
| <b><i>BRCA</i></b> | Breast Cancer Associated (Gene)       |
| <b>ER</b>          | Oestrogen                             |
| <b>HBOC</b>        | Hereditary Breast and Ovarian Cancer  |
| <b>HER2</b>        | Human Epidermal Growth Factor 2       |
| <b>LIMC</b>        | Low-to-Middle Income                  |
| <b>NCCN</b>        | National Comprehensive Cancer Network |
| <b>NHLS</b>        | National Health Laboratory Services   |
| <b>PR</b>          | Progesterone                          |
| <b>REDCap</b>      | Research Electronic Database Capture  |
| <b>SD</b>          | Standard deviation                    |
| <b>TNBC</b>        | Triple Negative Breast Cancer         |
| <b>USA</b>         | United States of America              |
| <b>VUS</b>         | Variant of Uncertain Significant      |

**Research report in the format of a “submissible” paper**

To be submitted to the South African Medical Journal

***An audit of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics***

Slindokuhle Sibiya<sup>1</sup> , Elzette Gilfillan<sup>1</sup> , Monica Araujo<sup>1</sup>

<sup>1</sup> Division of Human Genetics, National Health Laboratory Service and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, National Health Laboratory Services, Johannesburg, South Africa

Corresponding Author: Slindokuhle Sibiya

E-mail address: [slindokuhlesibiya8@gmail.com](mailto:slindokuhlesibiya8@gmail.com) / [2307784@students.wits.ac.za](mailto:2307784@students.wits.ac.za)

## **Abstract for Journal Submission**

**Background:** Breast cancer remains a leading cause of cancer-related deaths globally, with incidence rates steadily rising in South Africa over the past two decades. Despite efforts such as screening programs and predictive testing, early detection and treatment are hindered by delayed diagnoses, limited healthcare access, and socioeconomic challenges, particularly in low- to middle-income countries. Micro-level assessments, such as clinical audits, are essential to identify gaps and improve care strategies. This study aimed to construct a patient profile of genetic testing outcomes and sociodemographic factors for individuals who underwent genetic counselling for hereditary breast cancer over six years (September 2018–January 2024) at the National Health Laboratory Services (NHLS), Braamfontein.

**Methods:** Data from 619 patient files were extracted from the departmental REDCap database. Extracted variables included demographic, personal, family, and medical history, alongside genetic testing uptake and outcomes. Statistical analyses included descriptive statistics, Chi-squared tests, t-tests, ANOVA, and multiple regression modelling.

**Result:** The study included 619 participants. The cohort was separated into two subsets, these eligible for diagnostic testing (594/619, 95.96%) and those eligible for predictive testing (25/619, 4.04%). The demographics of the diagnostic testing subset mirrored those of the overall cohort, predominantly comprising Black participants, state-sector patients, and urban residents. Conversely, Black participants, state-sector patients, and unemployed participants were underrepresented in the subset eligible for predictive testing. Employment data was incomplete for 37.32% of the cohort, among those recorded, employed and unemployed participants were equally represented (~30% each). The uptake of diagnostic testing was 78.96%. Sociodemographic factors influenced diagnostic testing uptake and outcomes. A lower mean age at diagnosis ( $p = <0.01$ ) and employment ( $p = 0.05$ ) positively impacted testing acceptance, while Black ancestry ( $p = 0.03$ ) and older age ( $p = 0.04$ ) were associated with lower rates of actionable genetic outcomes. While the uptake of predictive testing was 88.00%, the number of relatives presenting for testing was low relative to the number of proband relatives eligible for predictive testing.

**Conclusion:** Understanding patient profiles and genetic testing trends is crucial for improving patient care and outcomes. This study highlights barriers such as healthcare challenges, research gaps, and limited awareness in hereditary breast cancer. Targeted efforts can enhance prevention, expand genetic testing, and address South Africa's rising breast cancer burden.

## **1. Background**

Cancer is a collective term that encompasses over 100 non-communicable diseases.<sup>[1]</sup> Affecting approximately 53.3 million people globally in 2022, cancer has become one of the most prevalent diseases and a leading cause of death globally.<sup>[2]</sup> The three most common cancers - lung, colorectal, and breast - accounted for over 6.7 million new cases and 34.9% of all cancer-related deaths across all sexes and age groups. The global cancer incidence is anticipated to surge by approximately 60% over the next two decades based solely on the projected population growth, with a significant proportion accounted for in Low- and Middle-Income Countries (LMICs).<sup>[3]</sup> Breast cancer, which predominantly affects women - accounting for ~30% of cancer cases, is reported as a significant contributor to the growing cancer burden. It accounted for 11.7% of new cancer cases in 2022 and has shown a rapid increase in number across both men and women globally.<sup>[4]</sup> Early diagnosis, timely intervention, and preventative measures have been identified as effective strategies to mitigate the burden of breast cancer.<sup>[5]</sup> The shift toward a more molecular understanding of cancer has also enabled the development of targeted therapies, immunotherapies, and personalised medicine approaches, further contributing to efforts to reduce the overall cancer burden.<sup>[6]</sup>

### ***1.1. The role of genetics in breast cancer***

While the majority of breast cancer cases are sporadic, approximately 5-10% are attributable to inherited pathogenic variants in cancer susceptibility genes which manifest as hereditary cancer syndromes.<sup>[7]</sup> These cases are marked by an early age of onset, a strong family history of related cancers, and bilateral disease presentation.<sup>[8]</sup> Hereditary Breast and Ovarian Cancer (HBOC) syndrome, primarily linked to BRCA1 and BRCA2 gene variants, respectively, is a significant contributor to the hereditary breast cancer burden. Carriers of these genes face a significantly elevated lifetime risk of several cancers, notably breast and ovarian cancers. Other high and moderate risk genes such as ATM, PALB2, and CHEK2 also contribute to hereditary breast cancer, conferring a significant predisposition risk, but still lower than that of BRCA1 and BRCA2.<sup>[9,10]</sup> Understanding these genetic contribution aids in identifying individuals with hereditary cancer risk through genetic counselling and testing, and is essential for guiding surveillance, risk-reducing strategies, and informing treatment. Importantly, these insights also allow for the identification and management of at-risk relatives.<sup>[6]</sup>

## ***1.2. Breast cancer in the South African context***

In South Africa, breast cancer remains the most commonly diagnosed cancer among women and one of the top causes of cancer-related mortality. From 2001 to 2020, newly diagnosed cases nearly tripled, rising from 5,668 to over 15,000 annually.<sup>[11]</sup> Dlamini et al., 2024 attributes this trend to delayed diagnosis, limited access to early detection services, low awareness, and health system constraints, particularly in the public sector. Although founder mutations in BRCA1 and BRCA2 have been well-documented in specific populations such as the Afrikaner and Ashkenazi Jewish communities, Black South Africans and other underrepresented groups remain poorly characterised in the genetic literature.<sup>[12]</sup> This has resulted in a high rate of variants of uncertain significance (VUSs) and limits the utility of test results for many individuals. Broader and more inclusive genomic data are urgently needed to ensure equitable care.<sup>[13]</sup>

## ***1.3. Access to Genetic services in South Africa***

Genetic counselling and testing services for hereditary breast cancer are offered through both the public and private healthcare sectors in South Africa. However, accessibility remains highly unequal. Clinical genetics services are concentrated in only a few provinces - primarily Gauteng, Western Cape, KwaZulu-Natal, and the Free State.<sup>[14]</sup> Private-sector patients typically benefit from better availability of services and fewer financial constraints, whereas public-sector patients face systemic barriers such as long referral pathways, limited awareness, understaffed genetic services, and funding shortages.<sup>[15,16]</sup> Even where genetic testing is available in state settings, uptake is often hindered by socioeconomic and cultural factors, as well as poor understanding of the implications of genetic results.<sup>[18]</sup>

Moreover, the uptake of predictive genetic testing - offered to healthy relatives of individuals with known familial variants - remains low in South Africa. Barriers include limited cascade testing protocols, inconsistent follow-up, and sociocultural factors that hinder intra-family communication of genetic risks.<sup>[19,20,21]</sup> As such, identifying patients eligible for predictive testing and ensuring follow-through remains a critical gap in the local healthcare landscape. Given this context, the role of clinical audits is increasingly important. Micro-level assessments can help generate locally relevant data, identify service gaps, and guide targeted interventions. Previous work has demonstrated the value of such audits in low-resource settings to optimise patient care and inform research and policy.<sup>[22]</sup>

### ***1.4. Rationale***

Despite the growing burden of breast cancer and the availability of genetic services in select South African centres, little is known about the sociodemographic trends in test uptake and the outcomes of genetic testing for hereditary breast cancer across diverse population groups. Central to this process is genetic counselling, which plays a critical role in ensuring informed decision-making, psychosocial support, and appropriate follow-up for individuals undergoing genetic testing. In the South African setting - marked by disparities in access to healthcare, limited resources, and low genetic literacy - the effectiveness of genetic counselling may be influenced by patient background, system constraints, and provider practices.

This study therefore aims to audit patient records from the Division of Human Genetics at the National Health Laboratory Services (NHLS), Braamfontein, between 2018 and 2024, to construct a profile of patients who underwent genetic counselling for hereditary breast cancer. By examining testing outcomes, patient sociodemographics, and referral reasons across both diagnostic and predictive contexts, the research provides insight into how genetic counselling services are currently delivered, who accesses them, and where gaps may exist. These findings can inform more equitable, context-appropriate strategies for counselling, education, and referral, ultimately supporting the broader integration of genetics into cancer care in South Africa.

## **2. Methods**

### ***2.1. Study participants and study setting***

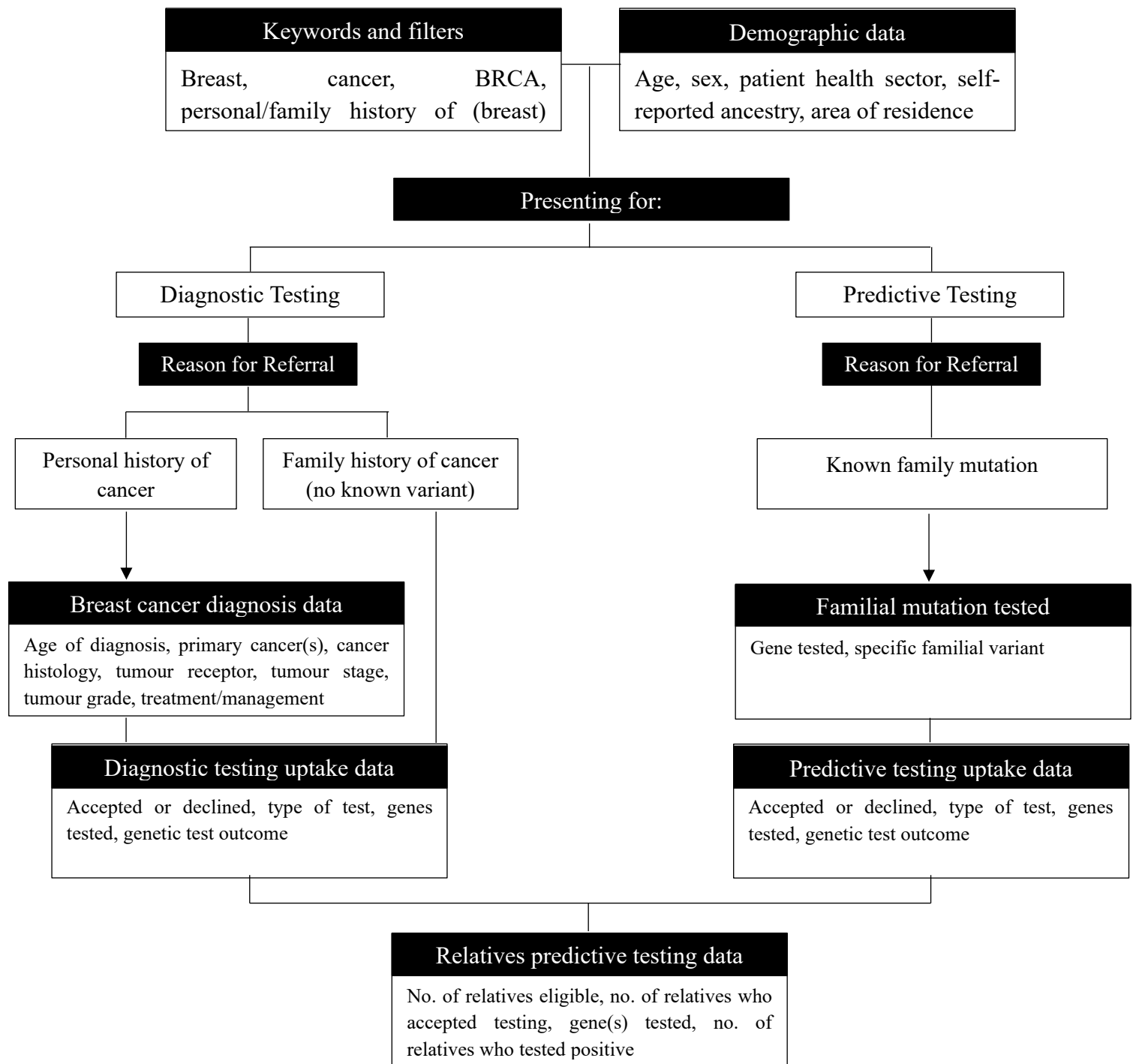
The study population included all available patient files of patients who presented for a genetic consultation for hereditary breast cancer with a registered genetic counsellor, medical geneticist, or genetic nurse between September 2018 and January 2024. The data collection begins specifically in September of 2018 as this is when the REDCap electronic database used for data collection in the study was established and implemented in the Division. All patients were individuals older than 18 years of age at the time of consultation and had a personal or family history of breast cancer. Individuals with incomplete Research Electronic Data Capture (REDCap) electronic files were excluded from the study. The REDCap database includes patient records from multiple breast cancer clinics, including Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Hospital, Potchefstroom Hospital, Helen Joseph Hospital, and Wits Donald Gordon Medical Centre.

## **2.2. Study design**

### *2.2.1. Data collection*

This study is a retrospective file review of patients seen for genetic consultation due to a personal or family history of breast cancer. Relevant patient files were retrieved using targeted keywords and filters. The data retrieved from patient files is summarised in **Figure 1**. A detailed data collection sheet can be found in **Appendix A**. The data collection sheet was created based on the REDCap database fields, to include all the sociodemographic, genetic testing, and cancer diagnoses information that had already been captured during the in-clinic genetic counselling sessions.

Sex was based on self-reported gender, with individuals self-identifying as either male, female, or other. Ancestry was defined by an individual's country of origin in combination to their ethnolinguistic group in accordance with the 12 official languages of South Africa. Area of residence was described as either urban formal or informal, semi-urban formal or informal, and rural formal or informal based on the Statistics South Africa, Census 2001 discussion document<sup>[20]</sup>. These variables were extracted from the REDCap patient records and recorded onto a Microsoft Excel Spreadsheet. All identifiers were excluded or subsequently removed from the data to ensure the anonymity of all the participants included in the study.



**Figure 1:** A summary of the data collected from each patient file extracted from the departmental REDCap clinical database

### 2.3. Statistical analysis

Data was stratified into continuous and categorical data. Categorical data was represented using percentages, and various graphical tools (bar charts, pie charts, and histograms). The continuous data was loaded onto the RStudio software program – normality of the continuous

variables was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov test, guided by the sample size of the variable being assessed. Normally distributed data was represented using means and standard deviations (SDs) and non-normally distributed data was represented using medians and interquartile ranges. The RStudio software program, was used to determine the presence of any significant associations between the variables. Chi-squared or Fishers exact tests were employed to evaluate potential associations between categorical variables, depending on the sample size with Chi squared test used for larger sample sizes ( $>5$ ) and Fishers exact test for smaller sample sizes ( $<5$ )., For investigations involving continuous variables, independent t-tests were used when the data is normally distributed, while or the Whitney Mann U Test were was utilised to investigate potential relationships between continuous variables when normality could not be assumed., Similarly, the one-way and an ANOVA was used when comparing continuous data across more than two groups where assumptions of normality and homogeneity of variance were met. In the case that these assumptions were not met, the non-parametric or Kruskal-Wallis test was used to assess possible relationships between continuous and categorical data.

Finally, non-confounding significant variables were included in a multiple regression model to identify key trends and associations – that were used to construct a profile of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics in the past six years. To determine whether a variable was a confounder, each variable was first checked for its association with both the exposure (variable suspected to influence the outcome) and the outcome (variable that the effect is being measured on) using simple regression models in the R statistics software. Variables that were significantly related to both were considered potential confounders. These were added to a multiple regression model to assess if they changed the effect of the main exposure variables. If the exposure-outcome relationship changes by more than 10%, the variable was considered a confounder. For statistical analyses, significance was assumed at a p value of  $< 0.05$ .

### **3. Results**

#### ***3.1. Study participants***

A total of 619 individuals who attended a genetic consultation for a personal and/or family history of breast cancer, including cases with a known familial variant, between September 2018 to January 2024 were included in the study. A total of 79 files were missing more than

20% of data (8 of the 40 data points) being collected in the study and were subsequently excluded from the study.

The study cohort demographics are summarised in **Table 1**. The study cohort was predominantly female individuals (596/619, 96.28%), with a mean age (SD) of 43.87 (10.96) years and a range of 19 to 83 years at the time of their consultation. Most individuals (539/619, 87.08%) received care at state healthcare facilities – with majority residing in urban areas, followed by semi-urban areas (52/619, 8.40%). The cohort predominantly consisted of Black individuals (424/619, 68.50%), followed by White (143/619, 23.10%) and Mixed ancestry (36/619, 5.82%) individuals. Employment data was incomplete for 231/619 (37.54%) of participants; however, among those with recorded data, 187/388 (48.20%) were employed, 183/388 (47.16%) were unemployed, and 18/388 (4.64%) were recorded as pensioners.

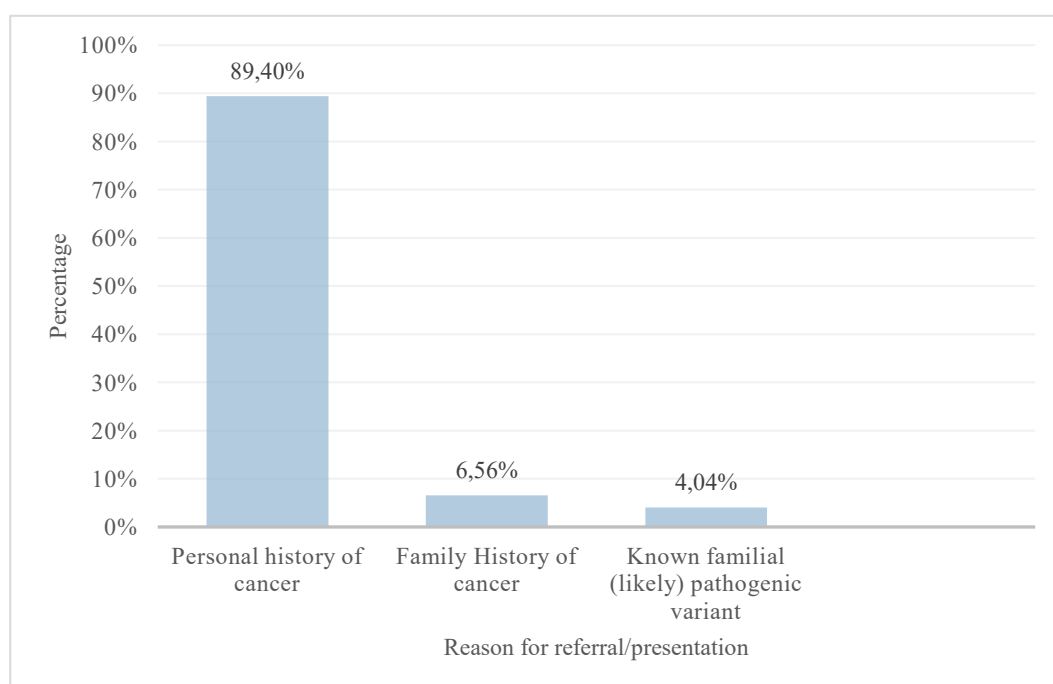
**Table 1: Demographic characteristics of the full study cohort, the ‘diagnostic testing’ subset, and the ‘predictive testing’ subset**

| <b>Characteristics</b>     | <b>Full cohort - N (%) or mean (SD)</b> | <b>Diagnostic testing subset - N (%) or mean (SD)</b> | <b>Predictive testing subset - N (%) or mean (SD)</b> |
|----------------------------|-----------------------------------------|-------------------------------------------------------|-------------------------------------------------------|
| <b>Sex</b>                 |                                         |                                                       |                                                       |
| Female                     | 596 (96.28)                             | 579 (97.48)                                           | 17 (68.00)                                            |
| Male                       | 23 (3.72)                               | 15 (2.53)                                             | 8 (32.00)                                             |
| <b>Age at consultation</b> |                                         |                                                       |                                                       |
| Mean age                   | 43.87 (10.96)                           | 43.88 (10.67)                                         | 43.52 (17.52)                                         |
| Range                      | 19 – 83                                 | 21 – 83                                               | 19 – 72                                               |
| <b>Age of diagnosis</b>    |                                         |                                                       |                                                       |
| Mean age                   | NA                                      | 41.58 (10.09)                                         | NA                                                    |
| Range                      | NA                                      | 21 – 83                                               | NA                                                    |
| <b>Sector</b>              |                                         |                                                       |                                                       |
| State                      | 539 (87.08)                             | 532 (89.56)                                           | 7 (28.00)                                             |
| Private                    | 80 (12.92)                              | 62 (10.43)                                            | 18 (72.00)                                            |
| <b>Ancestry</b>            |                                         |                                                       |                                                       |
| Black                      | 424 (68.50)                             | 422 (71.04)                                           | 2 (8.00)                                              |
| White                      | 143 (23.10)                             | 121 (20.37)                                           | 22 (88.00)                                            |
| Mixed                      | 36 (5.82)                               | 36 (6.06)                                             | 0.00                                                  |
| Indian                     | 14 (2.26)                               | 13 (2.19)                                             | 1 (4.00)                                              |
| Other *                    | 2 (0.32)                                | 2 (0.34)                                              | 0.00                                                  |
| <b>Area of residence</b>   |                                         |                                                       |                                                       |
| International              | 6 (0.97)                                | 6 (1.01)                                              | 0.00                                                  |
| Urban                      | 501 (80.94)                             | 481 (80.98)                                           | 20 (80.00)                                            |
| Semi-Urban                 | 52 (8.40)                               | 51 (8.59)                                             | 1 (4.00)                                              |
| Rural                      | 29 (4.68)                               | 28 (4.71)                                             | 1 (4.00)                                              |
| Semi-Rural                 | 13 (2.10)                               | 13 (2.19)                                             | 0.00                                                  |
| Incomplete information     | 18 (2.91)                               | 15 (2.52)                                             | 3 (12.00)                                             |
| <b>Employment</b>          |                                         |                                                       |                                                       |
| Employed                   | 187 (30.21)                             | 174 (29.30)                                           | 13 (52.00)                                            |
| Unemployed                 | 183 (29.56)                             | 179 (30.13)                                           | 4 (16.00)                                             |

|                        |             |             |           |
|------------------------|-------------|-------------|-----------|
| Pensioner              | 18 (2.91)   | 18 (3.03)   | 0.00      |
| Incomplete information | 231 (37.32) | 223 (37.54) | 8 (32.00) |

\* Pakistani, and Mozambican Portuguese

The cohort can be separated into two distinct subsets as seen in the third and fourth columns of **Table 1**, depending on the type of genetic testing relevant to the individual. The first subset is those eligible for diagnostic testing, which encompasses individuals presenting with a personal history of cancer, and those presenting with a family history of cancer including breast cancer (with no known familial variant). The second subset includes healthy individuals without any current or prior cancer diagnosis, presenting for testing due to a known familial variant, and are hence eligible for predictive testing. As illustrated in **Figure 2**, 594/619 (95.96%) participants fell into the first subset, and 25/619 (4.04%) fell into the second subset, based on the reason for referral/presentation.



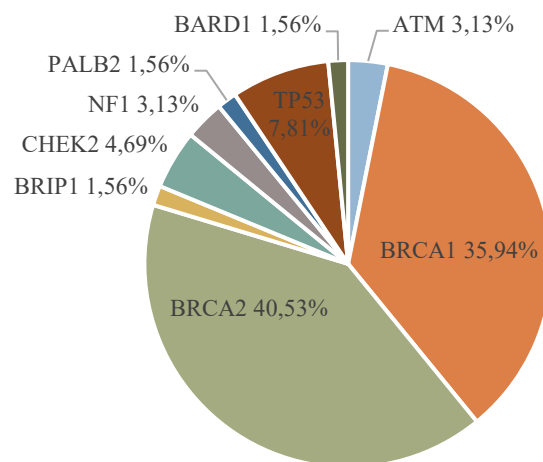
**Figure 2:** The distribution of reasons for referral to the genetic clinic across the study cohort

### ***3.2. Subset eligible for diagnostic genetic testing***

The subset of participants eligible for diagnostic (594/619, 95.96%) testing largely mirrored the demographic distribution of the full cohort, with most participants being female, of Black ancestry, receiving care in the state sector, and residing in urban areas, as summarised in **Table 1**.

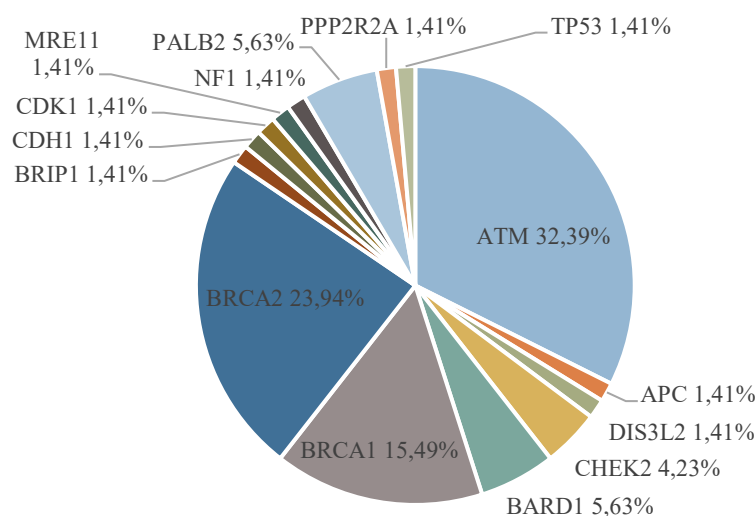
### 3.2.1. Diagnostic testing uptake and outcomes

Genetic testing was offered to all patients who were determined to be at moderate to high risk of having a hereditary cancer syndrome based on their personal and/or family history of cancer. A total of 469/594 (78.96%) individuals accepted testing with a smaller proportion – 125/594 (21.04%) declining testing during the genetic consultation. In the subgroup that accepted testing, a total of 426/469 (90.83%) of individuals had received a result back at the time of data collection, while 43/469 (9.17%) had yet to receive a result back. A total of 62/426 (30.29%) had actionable variant(s) identified, including likely pathogenic and pathogenic variants, summarised in **Figure 3**.



**Figure 3:** The distribution of actionable variants found across various genes included in the testing panel(s)

The rest of the cohort, 364/426 (85.44%) received a non-actionable result, encompassing 71 participants with variants of uncertain significant (VUSs), as illustrated in **Figure 4**.



**Figure 4:** The distribution of VUSs across various genes included in the testing panel(s)

### 3.2.2. Sociodemographic factors affecting diagnostic testing uptake and outcomes

Analysis of participant sociodemographic factors showed two main factors that possibly influenced diagnostic testing uptake and outcomes. As seen in **Table 2**, the association between employment status and the likelihood to decline or accept diagnostic testing approached significance ( $p = 0.058$ ) where employed participants were more likely to accept testing than their unemployed counterparts, and a significant association was observed between participants age of diagnosis and the likelihood to accept or decline diagnostic testing ( $p = 0.0061$ ), where younger participants were more likely to accept testing than older participants. Conversely, there was no difference between the health sector of participants that accepted or declined diagnostic testing ( $p = 0.40$ ), and males and females were equally likely to accept or decline testing ( $p = 1.00$ ). Additionally, participants of all ancestry groups had an equal likelihood of accepting or declining diagnostic testing ( $p = 0.52$ ), similar to participants of various residential areas ( $p = 0.53$ ), and those with unilateral or bilateral breast cancer, and the presence or absence of metastasis ( $p = 0.15$ ).

**Table 2:** A summary of factors showing a significant association with genetic testing uptake and outcomes

|                                 | Diagnostic genetic testing                  |                                         | p-value |
|---------------------------------|---------------------------------------------|-----------------------------------------|---------|
| <i>Genetic testing uptake</i>   |                                             |                                         |         |
|                                 | Accepted (n = 469)                          | Declined (n=125)                        |         |
| Employment Status               |                                             |                                         |         |
| Employed                        | 130 (27.72)                                 | 44 (35.20)                              | 0.055   |
| Unemployed                      | 143 (30.49)                                 | 36 (28.80)                              |         |
| Pensioner                       | 10 (2.13)                                   | 8 (6.40)                                |         |
| Incomplete information          | 186 (39.66)                                 | 37 (29.60)                              |         |
| Mean age of diagnosis (years)   | 40.9 ± 9.47                                 | 44.3 ± 11.9                             | 0.0061  |
| <i>Genetic testing outcomes</i> |                                             |                                         |         |
|                                 | No actionable variants identified (n = 364) | Actionable variants identified (n = 62) |         |
| Ancestry                        |                                             |                                         |         |
| Black                           | 269 (73.90)                                 | 29 (46.77)                              | 0.003   |
| White                           | 67 (18.41)                                  | 26 (41.94)                              |         |
| Mixed ancestry                  | 22 (6.04)                                   | 2 (3.23)                                |         |
| Indian                          | 4 (1.10)                                    | 5 (8.06)                                |         |
| Other                           | 2 (0.55)                                    | 0                                       |         |
| Age of diagnosis (years)        |                                             |                                         |         |
| <30                             | 30 (8.24)                                   | 9 (14.52)                               | 0.03    |
| 30 – 50                         | 290 (79.67)                                 | 42 (67.74)                              |         |

|     |            |            |  |
|-----|------------|------------|--|
| >50 | 44 (12.09) | 11 (17.74) |  |
|-----|------------|------------|--|

Similarly, as summarised in **Table 2**, participant sociodemographic factors were assessed against genetic testing outcomes. Ancestry ( $p = 0.03$ ) and age of diagnosis ( $p = 0.04$ ) – showed significant associations with genetic testing outcomes. Notably, individuals of Black ancestry were more likely to receive a ‘no actionable variants identified’ outcomes, and individuals in the >30 years age group had the least likelihood of receiving a ‘no actionable variants identified outcome’. Other factors, including sex ( $p = 0.76$ ), and primary cancer ( $p = 0.07$ ), showed no association with participant genetic testing outcome.

### ***3.2. Subset eligible for predictive genetic testing***

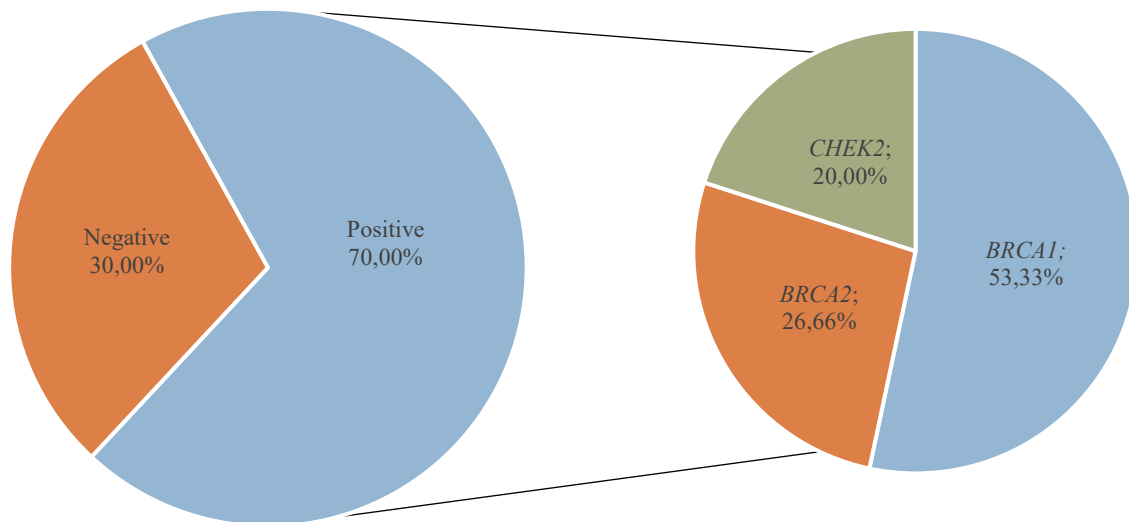
The predictive testing subset showed distinct demographic characteristics, as outlined in **Table 1**. A total of 123 relatives of proband patients seen and tested through the Division of Human Genetics were identified to be at-risk and of legal age (18 years), and were hence eligible for predictive testing. Of this total, 32/123 (26.02%) at-risk relatives underwent predictive testing over the six years; however, only 25/32 (78.13%) were seen for predictive testing through Division, with the remaining 7/32 (21.88%) reported by proband patients as having been tested externally. Consequently, genetic testing data is only available for the 25 at-risk relatives seen through the Division of Human Genetics.

Females accounted for the majority (17/25, 68.00%) of this group, with a mean age of  $43.52 \pm 17.52$  years (range: 19–72) at the time of their consultation. More than half (18/25, 72.00%) sought care in private healthcare facilities, while 7/25 (28.00%) were managed in the state sector. Additionally, this subset was predominantly White (22/25, 88.00%), followed by Black (2/25, 8.00%) and Indian (1/25, 4.00%) ancestry participants with no Mixed ancestry participants recorded. Most resided in urban areas (20/25, 80.00%), with smaller proportions from rural semi-urban (1/25, 4.00%) and rural (1/25, 4.00%) areas. Employment data was unavailable for 8/25 (32.00%) of this subset, however, among recorded cases; 13/17 (76.47%) were employed and 4/17 (23.63%) were unemployed.

#### ***3.2.1. Predictive testing uptake and outcomes***

Genetic testing was offered to all patients with a known pathogenic or likely pathogenic variant identified by molecular genetic testing in a family member. A total of 22/25 (88.00%) participants accepted testing with a smaller proportion – 3/25 (12.00%) declining testing during the genetic counselling consultation. Of those who had accepted testing, a total of 20/22

(90.91%) had received a result back at the time of data collection, while 2/22 (9.09%) did not have a result available yet. The genetic test results outcomes are summarised in **Figure 5**. A total of 6/20 (30.00%) tested negative for the familial variant, with the rest (14/20, 70.00%) being positive for the familial variant. Majority of the predictive testing was done for and identified variants in *BRCA1* (7/14, 50.00), followed by *BRCA2* (3/14, 21.43%), and *CHEK2* (3/14, 21.43%), with a single participant testing positive or pathogenic variants in both *BRCA1* and *BRCA2*.



**Figure 5:** A summary of diagnostic test outcomes for the individuals that accepted diagnostic testing, showing the proportion of those with no actionable variants identified and the various variants identified in those with actionable results

#### **4. Discussion**

This study indicates a high uptake of diagnostic and predictive genetic testing among participants who attended genetic consultations. However, when considering the number of relatives eligible for predictive testing over six years and those who actually presented for predictive testing, the overall uptake of predictive testing within the Division remains low, despite the high acceptance rate among those who did present. Participants with a personal history of cancer were disproportionately represented compared to those with a family history, the latter represented by only a small group of participants. Sociodemographic factors influenced diagnostic testing uptake and outcomes. A lower mean age at diagnosis and employment positively impacted testing acceptance, while Black ancestry and older age were associated with lower rates of actionable genetic outcomes. Additionally, Black participants and state-sector patients were underrepresented among those eligible for predictive testing.

While the study effectively assessed patient sociodemographics and genetic testing trends in a well characterised and representative cohort, several limitations were noted. A key limitation was the inconsistency in data entry throughout the iterative development of the REDCap database, leading to variations in recorded information over the six-year data collection period. This meant that the data entries from the beginning of the data collection period varied considerably from those at the end of the data collection period. Earlier records often lacked key demographic and clinical variables, necessitating the exclusion of these files. Additionally, to enable meaningful analysis, the cohort was divided into two subsets, allowing for focused examination but resulting in a reduced sample size for any robust statistical analysis in one subset. This limited the strength of statistical inferences and the ability to detect associations.

Consistent with previous studies assessing access and resource utilisation in healthcare, urban residents comprised the majority of this study's cohort. This finding is consistent with the defining resource availability in urban and rural regions, which significantly impact access and health-seeking behaviours<sup>[22, 23]</sup>. Urban areas are characterised by extensive infrastructure and services, whereas rural areas are generally geographically isolated and depend on neighbouring towns for resources such as healthcare facilities. This centralisation, coupled with rural inaccessibility, likely contributes to the low utilisation of genetic services observed in rural populations<sup>[22, 24]</sup>.

Challenges at the primary care level contribute to the predominance of patients referred for a personal history of cancer over those with a family history. Studies attribute this disparity to primary care providers who are responsible for initiating specialist referrals but are often limited to short patient visits and lack the training to collect an extensive family history which hinders the assessment of hereditary cancer risk<sup>[25]</sup>. Consequently, those without a personal history, which suggests an obvious risk, are overlooked for referral to specialists such as genetic counsellors. Furthermore, unawareness of family history - particularly among Black women with breast cancer<sup>[26]</sup>, often due to limited family health communication and inadequate healthcare access - may lead to family history cases being misclassified as personal history. Together, these factors reinforce the higher proportion of personal history cases observed.

Assessing the diagnostic genetic testing trends in South Africa remains challenging due to the limited number of studies addressing this topic. Mukendi-Ilunga et al, 2023 reported a diagnostic genetic testing uptake rate of 87.18% among patients diagnosed with invasive breast carcinomas, while an earlier study by Schoeman et al, 2013 found an uptake rate of only 14.9%

among a diverse patient population treated for breast cancer<sup>[28]</sup>. The findings of this study align with the more recent report, both indicating notably high uptake rates compared to the study conducted ten years prior. This observation reveals a significant temporal improvement in genetic testing uptake in South Africa, with an increase of 72.28% over just ten years.

This improvement, particularly when compared to countries like the United States of America (USA), which reports low uptake rates (~40%), can partially be attributed to state subsidisation programs<sup>[17]</sup>. In South Africa, subsidised patients benefit from partial or full coverage of healthcare costs by the state<sup>[29]</sup>. This significantly lowers the financial barrier to genetic testing, enabling broader access and could potentially be contributing to the observed rise in uptake rates. Gradual development in the genetics field, supported by awareness campaigns and educational initiatives, also contributes to increased uptake<sup>[30]</sup>. Wessels et al, 2024 suggest that as these initiatives continue to raise the public and professional understanding of genetic services an accompanying increase in diagnostic genetic testing uptake is expected<sup>[28]</sup>.

Diagnostic genetic testing outcomes were consistent with past literature, with *BRCA1* and *BRCA2* pathogenic variants being the most common. Notably, a frequent non-actionable outcome was a VUS in the *ATM* gene. This aligns with several South African studies where participants with VUSs in the *ATM* gene frequently dominate genetic testing outcomes, reflecting the gene's highly polymorphic nature which makes it challenging to determine variant pathogenicity<sup>[31]</sup>. This observation can also be linked to the transition from targeted *BRCA1/BRCA2* testing to broader genetic panels, inherently increasing the likelihood of identifying a VUS<sup>[32]</sup>. Black ancestry was associated with 'no actionable variants identified' results, highlighting underrepresentation of this population in genomic studies and databases. This exacerbates challenges in variant classification, particularly for complex genes like *ATM*, as factors such as allele frequency often remain unknown contributing to higher rates of inconclusive outcomes<sup>[33]</sup>.

Similar to previous studies from the USA, and Brunei - the mean age of diagnosis influenced diagnostic testing uptake and outcomes. Similar to this study, Pederson & Narod (2024), noted an older age of diagnosis to be a barrier to genetic testing due to factors such as a lack of awareness, and general mistrust of the medical system amongst older patients<sup>[17]</sup>. This was corroborated by a cross-sectional study in Brunei that reported that younger participants (18 – 29 years) had a better knowledge and more positive attitudes towards genetic testing compared to those aged 50 and above, which may explain the higher uptake of genetic testing in those

with a lower mean age of diagnosis<sup>[34]</sup>. Furthermore, younger participants (<30 years) were less likely to receive a 'no actionable variants identified' result, aligning with the well-established link between a younger age of onset (<50 years) and an increased risk of hereditary breast cancer, as hereditary syndromes often manifest earlier in life<sup>[35]</sup>. This may reflect ascertainment bias, where younger individuals are more readily classified as high-risk for hereditary cancer syndromes and are therefore prioritised for genetic counselling and testing, leading to a higher identification of actionable variants in this group.

Employment status emerged as a potential determinant of diagnostic genetic testing uptake. Consistent with previous research, employed individuals were more likely to accept genetic testing compared to their unemployed counterparts.<sup>[36]</sup> Hosseinpour et al, 2012 note that employed individuals, often younger and more educated, demonstrated better health literacy and proactive health-seeking behaviours, increasing their likelihood of accepting testing<sup>[37]</sup>. Contrary to several studies, the health sector did not significantly influence participants' decisions to accept or decline testing in this study. Maseko et al, 2018 noted that public perceptions of private hospitals as offering better care and empowerment often led to higher rate of testing uptake in private settings, compared to state hospitals associated with neglect and abusive staff<sup>[38]</sup>. However, the lack of a significant difference in this study suggests that other factors, such as age or employment status, may have had a stronger influence on participants' decision-making regarding genetic testing.

Notable demographic differences in the predictive testing subset included an overrepresentation of individuals of White ancestry and private-sector patients, reflecting research that highlights minority underrepresentation in genetic studies and its impact on predictive testing uptake<sup>[39]</sup>. Hesse-Biber et al, 2023 found that non-Hispanic White individuals were more likely to share their genetic test results with family and friends compared to Black, Indigenous, and people of colour (BIPOC). The BIPOC group demonstrated higher rates of personal discrimination, resilience, and lower patient activation scores, all of which contributed to their reluctance to share genetic test results<sup>[17]</sup>. This, in turn, led to lower rates of predictive testing uptake within these populations, and could potentially explain the paucity of other ancestry groups, particularly the Black ancestry group, in the predictive testing subset. Moreover, disparities in South Africa's two-tiered healthcare system, where private-sector patients have better access to preventative care, contributes to the high proportion of private patients in this subset.<sup>[20]</sup> Conversely, the public sector, burdened with high service demand and limited resources, must prioritise acutely ill patients over preventative interventions. Such

differences may explain the low representation of public sector patients in this subset, as genetic testing for predictive purposes is less accessible within the state healthcare system<sup>[15]</sup>.

Despite the relatively high uptake of predictive testing among relatives of probands seen at the breast clinics, the number of relatives presenting for predictive testing remains low compared to those eligible for predictive testing. Foster et al, 2002 suggested that the uncertainty surrounding predictive testing for breast and ovarian cancer, where an individual carrying a pathogenic variant in a breast and ovarian cancer susceptibility gene may develop breast cancer, ovarian cancer, both cancers, or neither, has discouraged individuals from genetic testing for HBOC unless an obvious risk is presented by diagnosis which classifies them as high risk for HBOC<sup>[19]</sup>. Moreover, the communication approach, whether direct (proband directly communicates result with high-risk relatives), indirect (proband consents for clinician to communicate result to high-risk relatives) or assisted (clinician provides a ‘family-friendly’ letter for proband to distribute), impacts uptake<sup>[19]</sup>. The effectiveness of the assisted approach utilised in the Division hinges on the proband's willingness and ability to engage their relatives, which may be hindered by cultural or emotional factors, and is a potential contributor to the low uptake of predictive testing observed<sup>[20]</sup>.

These findings offer actionable insights to strengthen epidemiological data on hereditary breast cancer in South Africa by highlighting patterns in genetic counselling uptake, referral practices, and testing outcomes across diverse population groups. They identify specific areas in need of improvement, such as addressing gaps in genetic literacy, improving access to services, and ensuring more equitable delivery of genetic counselling. The data can guide clinicians and researchers in directing education and research initiatives toward underserved or underrepresented demographics, increasing awareness of hereditary breast cancer and the importance of genetic testing as part of broader cancer control strategies. In a country as diverse as South Africa, examining population-level trends at a micro level enables the development of tailored, context-appropriate solutions, particularly where insights from other settings may not be directly applicable.

Further studies, encompassing a larger study cohort and specifically assessing those presenting for predictive testing can provide more insight into the specific barriers to predictive testing in the division and country at large. These could aid in establishing a predictive testing model and approach specific and appropriate to our unique setting in order to maximise utilisation of the services and encourage preventative care.

## **5. Conclusion**

Understanding the patient profile and genetic testing trends is essential for guiding education, research, and quality strategies that target focus areas to enhance patient care and outcomes. With the rising breast cancer burden in South Africa, it is imperative to assess existing processes and address gaps that hinder early detection, timely treatment, and preventative care – particularly for hereditary breast cancer. This study identifies patient factors, healthcare system challenges, and research gaps as major barriers. Engaging specific communities through relevant and appropriate channels and addressing the lack of research on underrepresented populations are vital steps towards raising awareness, increasing acceptance of genetic testing, and making genetics applicable and accessible to a broader demographic. Moreover, the findings suggests that the state has yet to fully leverage the role of genetics in addressing breast cancer. While hereditary cases represent a small proportion, genetic insights can play a pivotal role in prevention by identifying at-risk family members and implementing early interventions. Concentrating efforts on these areas can drive better patient outcomes ad contribute to mitigating the growing breast cancer burden in South Africa.

## **6. Declarations**

### **Statements of Ethics**

Ethics approval was granted by the Human Research Ethics Committee (HREC) Medical, University of the Witwatersrand (Certificate number: M240613). (*Appendix A*)

### **Conflict of Interests Statement**

The authors have no conflicts of interest to declare.

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## **Appendices**

Appendix A: Detailed data collection sheet

Appendix B: Supplementary Tables and Figures

Appendix C: Ethics clearance certificate

Appendix D: Approved Research Protocol

Appendix E: Turnitin Report and Plagiarism Declaration

Appendix F: Author Guidelines for *South African Medical Journal*

## *Appendix A: Detailed data collection sheet*

### **DEMOGRAPHICS**

Date of birth

\_\_\_\_\_

Employment status

- ☐ Employed  
☐ Unemployed

Financial classification

- ☐ H0  
☐ H1  
☐ H2  
☐ H3

Self-reported ancestry

- ☐ White European  
☐ White Afrikaner  
☐ White Ashkenazi Jewish  
☐ Black Zulu  
☐ Black SePedi  
☐ Black Xhosa  
☐ Black Setswana  
☐ Black Tshivenda  
☐ Black SiSwati  
☐ Black Ndebele  
☐ Black SeSotho  
☐ Indian  
☐ Asian

Area of residence

- ☐ Rural area  
☐ Urban area

### **CANCER**

Date of test and/or genetic counselling

\_\_\_\_\_

Cancer History

- ☐ Yes  
☐ No

Tumour Type

- ☐ Benign  
☐ Malignant

Age at diagnosis

\_\_\_\_\_

Primary Cancers

- ☐ Unilateral Breast
- ☐ Bilateral Breast
- ☐ Unilateral Ovarian
- ☐ Bilateral Ovarian
- ☐ Endometrial/Uterine
- ☐ Colorectal
- ☐ Pancreatic
- ☐ Prostate
- ☐ Melanoma
- ☐ Brain
- ☐ Thyroid
- ☐ Retinoblastoma
- ☐ Haematological
- ☐ Other

Specify

Breast Cancer Histology

- ☐ Invasive ductal carcinoma
- ☐ Invasive carcinoma unspecified
- ☐ Ductal carcinoma in situ
- ☐ Lobular carcinoma
- ☐ Medullary carcinoma
- ☐ Metaplastic carcinoma
- ☐ Mucinous carcinoma
- ☐ Cribriform carcinoma
- ☐ Tubular carcinoma
- ☐ Pleomorphic carcinoma
- ☐ Neuroendocrine carcinoma
- ☐ Apocrine carcinoma
- ☐ Other

Specify

Breast Tumour Receptor Status

- ☐ Luminal A (ER+, PR+, HER2-, ki67low)
- ☐ Luminal B [HER2-] (ER+, PR-, HER2-, ki67high)
- ☐ Luminal B [HER2+] (ER+, PR-/+, HER2+, ki67lowhigh)
- ☐ HER2+(ER-, PR-, HER2+, ki67high)
- ☐ Triple negative (ER-, PR-, HER2-, ki67high)

Tumour Stage

\_\_\_\_\_

Tumour Grade

\_\_\_\_\_

Metastatic

- ☐ Yes
- ☐ No

Site(s)

- ☐ Liver
- ☐ Lung
- ☐ Bone
- ☐ Other

**PERSONAL HISTORY**

Diagnostic testing

- ☐ Yes  
☐ No

Type of test

- ☐ Single gene  
☐ Gene panel

Type of gene panel

- ☐ BRCA 1 and BRCA 2  
☐ 15-gene Bloem panel  
☐ 8-gene Bloem panel  
☐ Inherited diseases panel  
☐ Ampath  
☐ Invitae  
☐ Other

Additional comments

Treatment/Management Before Genetic Test Result

- ☐ Surgery  
☐ Radiation  
☐ Chemotherapy  
☐ Targeted hormone therapy  
☐ Chemoprevention  
☐ Palliative  
☐ None

Type of surgery

- ☐ Lumpectomy  
☐ Mastectomy  
☐ Salpingo-oophorectomy

Result

- ☐ Positive  
☐ VUS  
☐ Negative

Result summary

Treatment/Management After Genetic Test Result

- ☐ Surgery  
☐ Radiation  
☐ Chemotherapy  
☐ Chemoprevention  
☐ Palliative  
☐ Targeted hormone therapy

Type of surgery

- ☐ Lumpectomy  
☐ Mastectomy  
☐ Targeted hormone therapy

## PREDICTIVE TESTING

Predictive testing

- ☐ Yes  
☐ No

Gene tested

- ☐ ATM  
☐ BARD1  
☐ BRCA1  
☐ BRCA2  
☐ BRIP1  
☐ CDH1  
☐ CHEK2  
☐ DICER1  
☐ EPCAM  
☐ MLH1  
☐ MSH2  
☐ MSH6  
☐ NF1  
☐ PALB2  
☐ PMS2  
☐ PTEN  
☐ RAD51C  
☐ RAD51D  
☐ SMARCA4  
☐ STK11  
☐ TP53

Familial variant tested for

\_\_\_\_\_

Test results

- ☐ Positive  
☐ Negative

## FAMILY HISTORY

Family pedigree

Number of first-degree female relatives

\_\_\_\_\_

Number of first-degree male relatives

\_\_\_\_\_

Number of second-degree relatives on maternal side

\_\_\_\_\_

Number of second-degree relatives on paternal side

\_\_\_\_\_

Number of relatives under 50

\_\_\_\_\_

### **CASCADE TESTING**

Number of relative eligible for genetic testing

\_\_\_\_\_

Number of relatives who accepted genetic counselling  
and testing

\_\_\_\_\_

Reason for testing

\_\_\_\_\_

Number of relatives who tested positive for the  
pathogenic/likely pathogenic variant

\_\_\_\_\_

### **LINKED FILES**

Linked REDCap ID

\_\_\_\_\_

**Appendix B: Supplementary Tables and Figures**

**Table S1:** A summary of factors showing no significant association with genetic testing uptake and outcomes

|                               | Diagnostic genetic testing                         |                                                |                |
|-------------------------------|----------------------------------------------------|------------------------------------------------|----------------|
| <i>Genetic testing uptake</i> |                                                    |                                                | <b>p value</b> |
|                               | <b>Accepted (n = 469)</b>                          | <b>Declined (n=125)</b>                        |                |
| <b>Sex</b>                    |                                                    |                                                |                |
| Females                       | 457 (97.44)                                        | 122 (97.60)                                    | 1.00           |
| Males                         | 12 (2.56)                                          | 3 (2.40)                                       |                |
| <b>Health Sector</b>          |                                                    |                                                |                |
| State                         | 417 (88.91)                                        | 115 (92.00)                                    | 0.40           |
| Private                       | 52 (11.09)                                         | 10 (8.00)                                      |                |
| <b>Ancestry</b>               |                                                    |                                                |                |
| Black                         | 326 (69.51)                                        | 96 (76.8)                                      | 0.52           |
| White                         | 103 (21.96)                                        | 18 (14.40)                                     |                |
| Mixed ancestry                | 27 (5.76)                                          | 9 (7.20)                                       |                |
| Indian                        | 11 (2.35)                                          | 2 (1.60)                                       |                |
| Other                         | 2 (0.43)                                           | 0 (0.00)                                       |                |
| <b>Residential Area</b>       |                                                    |                                                |                |
| Urban                         | 374 (79.10)                                        | 107 (85.60)                                    | 0.53           |
| Semi-urban                    | 43 (9.17)                                          | 8 (6.40)                                       |                |
| Rural                         | 25 (5.33)                                          | 3 (2.40)                                       |                |
| Semi-rural                    | 10 (2.13)                                          | 3 (2.40)                                       |                |
| Incomplete information        | 17 (3.62)                                          | 4 (3.20)                                       |                |
| <b>Primary Cancer(s)</b>      |                                                    |                                                |                |
| Unilateral                    | 418 (89.13)                                        | 109 (87.20)                                    | 0.38           |
| Bilateral                     | 23 (4.90)                                          | 3 (2.40)                                       |                |
| Incomplete information        | 28 (5.97)                                          | 13 (10.40)                                     |                |
| <b>Metastasis</b>             |                                                    |                                                |                |
| Yes                           | 65 (13.86)                                         | 24 (19.20)                                     | 0.15           |
| No                            | 350 (74.63)                                        | 85 (68.00)                                     |                |
| Incomplete information        | 54 (11.51)                                         | 16 (12.80)                                     |                |
|                               | <b>No actionable variants identified (n = 364)</b> | <b>Actionable variants identified (n = 62)</b> | <b>p-value</b> |
| <b>Sex</b>                    |                                                    |                                                |                |

|                                 |             |            |       |
|---------------------------------|-------------|------------|-------|
| Females                         | 355 (97.53) | 61(98.39)  | 0.76  |
| Males                           | 9 (2.47)    | 1 (1.61)   |       |
| <b>Ancestry</b>                 |             |            |       |
| Black                           | 269 (73.90) | 29 (46.77) | 0.003 |
| White                           | 67 (18.41)  | 26 (41.94) |       |
| Mixed ancestry                  | 22 (6.04)   | 2 (3.23)   |       |
| Indian                          | 4 (1.10)    | 5 (8.06)   |       |
| Other                           | 2 (0.55)    | 0          |       |
| <b>Primary Cancer(s)</b>        |             |            |       |
| Unilateral                      | 326 (89.56) | 54 (87.10) | 0.06  |
| Bilateral                       | 15 (4.12)   | 6 (9.68)   |       |
| Incomplete information          | 23 (6.32)   | 2 (3.23)   |       |
| <b>Age of diagnosis (years)</b> |             |            |       |
| <30                             | 30 (8.24)   | 9 (14.52)  | 0.03  |
| 30 – 50                         | 290 (79.67) | 42 (67.74) |       |
| >50                             | 44 (12.09)  | 11 (17.74) |       |

## Appendix C: Ethics Clearance Certificate



R14/49 Miss Slindokuhle Sibiya M240613 MED24-04-577

### **HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)** **CLEARANCE CERTIFICATE NO. M240613 MED24-04-577**

**NAME:** Miss Slindokuhle Sibiya  
**(Principal Investigator)**

**STUDENT/STAFF NO:** 2307784

**DEGREE:** MSc Genetic Counselling

**DEPARTMENT:** School of Pathology  
Human Genetics  
NHLS

**PROJECT TITLE:** An audit of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics over a 6-year period

**DATE CONSIDERED:** 21/06/2024

**DECISION:** Approved unconditionally

**CONDITIONS:**

**SUPERVISOR:** Miss Monica Araujo and Mrs Elzette Gilfillan

**APPROVED BY:** Paul Ruff  
Paul Ruff (Aug 5, 2024 15:18 GMT+2)  
Prof P Ruff, Chair, HREC (Medical)

**DATE OF APPROVAL:** 29/07/2024    **EXPIRY DATE:** 29/07/2029

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

#### **DECLARATION OF INVESTIGATORS**

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to Committee. **I agree to submit a yearly progress report** in July each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year. Unreported changes to the application invalidate the clearance given by the HREC (Medical). Email signed copy of this ethics clearance certificate prior to commencing with the study [hrec-medical.researchoffice@wits.ac.za](mailto:hrec-medical.researchoffice@wits.ac.za)

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

***Appendix D: Approved Research Protocol***



Private Bag 3 Wits, 2050  
Fax: 027117172119  
Tel: 02711 7172076

Reference: Ms Sandra Munesar  
E-mail: [Sandra.munesar@wits.ac.za](mailto:Sandra.munesar@wits.ac.za)

13 August 2024  
Person No: 2307784  
PAG

Miss SA Sibiya  
3 Yellowwood Street  
Mphushini Park  
Mpushini Park  
3815  
South Africa

Dear Miss Slindokuhle Sibiya

**Master of Science in Medicine: Approval of Title**

We have pleasure in advising that your proposal entitled *An audit of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Sandra'.

Ms Sandra Munesar  
Faculty Registrar  
Faculty of Health Sciences

|                                                                                                                                                                                                                              |                          |                                                   |  |                                |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------|--|--------------------------------|--|
| CANDIDATE'S SURNAME: <b>Sibiya</b>                                                                                                                                                                                           |                          | FIRST NAME/S: <b>Slindokuhle Angel</b>            |  | STUDENT NUMBER: <b>2307784</b> |  |
| CURRENT QUALIFICATIONS: <b>BHSc (Med) Human Genetics</b>                                                                                                                                                                     |                          |                                                   |  |                                |  |
| TEL: <b>011 489 9227</b>                                                                                                                                                                                                     | CELL: <b>063 72 6456</b> | E-MAIL: <b><u>2307784@students.wits.ac.za</u></b> |  | FAX:                           |  |
| DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: <b>MSc (Med) Genetic Counselling</b>                                                                                                                                           |                          |                                                   |  |                                |  |
| PART-TIME OR FULL-TIME: <b>Full-time</b>                                                                                                                                                                                     |                          |                                                   |  |                                |  |
| FIRST REGISTERED FOR THIS DEGREE: <b>2024</b>                                                                                                                                                                                |                          | TERM : <b>1</b>                                   |  | YEAR: <b>2024</b>              |  |
| DEPARTMENT: <b>Human Genetics</b>                                                                                                                                                                                            |                          |                                                   |  |                                |  |
| TITLE OF PROPOSED RESEARCH:<br><br><b>An audit of genetic testing outcomes and sociodemographic factors of patients who received genetic counselling for hereditary breast cancer through the Division of Human Genetics</b> |                          |                                                   |  |                                |  |
| CANDIDATE'S SIGNATURE: <i>SAS</i>                                                                                                                                                                                            |                          |                                                   |  | DATE: <b>21/05/2024</b>        |  |
| SUPERVISOR 1 (NAME & SURNAME): <b>Monica Araujo</b>                                                                                                                                                                          |                          |                                                   |  | 60% Supervision                |  |
| SUPERVISOR'S QUALIFICATIONS: <b>MSc (Med) Genetic Counselling</b>                                                                                                                                                            |                          |                                                   |  |                                |  |
| SUPERVISOR'S DEPARTMENT: <b>Human Genetics</b>                                                                                                                                                                               |                          |                                                   |  |                                |  |
| SUPERVISOR'S ADDRESS / TEL / E-MAIL: <b>Room 6, First floor, Jack Metz Building, Cnr Hospital and De Korte Street, Braamfontein   [T]: 011 489 9902/9223   [E]: monica.araujo@nhls.ac.za</b>                                 |                          |                                                   |  |                                |  |
| SUPERVISOR 2 (NAME & SURNAME): <b>Elzette Gilfillan</b>                                                                                                                                                                      |                          |                                                   |  | 40% Supervision                |  |
| SUPERVISOR'S QUALIFICATIONS: <b>MSc (Med) Genetic Counselling</b>                                                                                                                                                            |                          |                                                   |  |                                |  |
| SUPERVISOR'S ADDRESS / TEL / E-MAIL: <b>Room 11, First floor, Jack Metz Building, Cnr Hospital and De Korte Street, Braamfontein   [T]: 011 489 9151/9223   [E]: elzette.nienaber@nhls.ac.za</b>                             |                          |                                                   |  |                                |  |

**SYNOPSIS OF RESEARCH:** (Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s)

**Introduction and Justification:**

The World Cancer Research Fund International (2022) reports cancer as one of the leading causes of death globally, with breast cancer being a significant contributor – accounting for 11.7% of cancer cases. Preventative strategies, including global population-level screening programs and family predictive testing (Marteri et al., 2022), have been implemented to mitigate the burden of breast cancer, a recognised national priority (Dlamini et al., 2023). However, despite this declaration and the efforts exerted to mitigate cancer burden, breast cancer incidence has witnessed a steady increase in the past decades (Dickens et al., 2016). This disparity between applied efforts and perceived outcomes prompts the need to assess the multifaceted aspects that make up the genetic testing landscape for breast cancer diagnostics, in order to identify factors contributing to the diminished efficacy of current systems, thereby exacerbating the cancer burden. Clinical audits are a crucial tool for establishing longitudinal data repositories, which play a pivotal role in identifying areas needing improvement, thereby directing the implementation of education, research, and quality improvement strategies to improve patient care and outcomes. Retrospective audits in particular, offer insights into historical benchmarks, in order to inform future research initiatives and improvement strategies (Esposito & Canton, 2014).

**Aim:**

To review files of patients referred for genetic counselling for a personal and/or family history of breast cancer through the Clinical and Counselling Unit in the Division of Human Genetics from 2018 to 2024.

**Methodology:**

The study entails the collection and analysis of all patient files seen for a genetic counselling consultation for hereditary breast cancer between September 2018 to January 2024. Records meeting the inclusion criteria will be selected and information pertaining to patient's demographics, personal, family, and medical history, financial and residential standing, and tumour histopathological features will be extracted and recorded into a REDCap database. The data will then be statistically analysed using various statistical analysis tools to analyse various associations and construct a patient profile and gain insight into the breast cancer diagnostics landscape in the division.

WITS ETHICS NOT REQUIRED:

Yes No

WITS ETHICS PENDING:

☒ Yes No

WITS ETHICS APPROVED:

Yes No

(circle appropriate symbol)\*

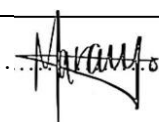
IF Y SUPPLY ETHICS

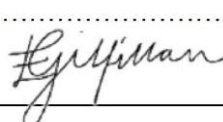
CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:

**\*Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**

**As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.**

SIGNATURE OF SUPERVISOR/S:

.....

.....

SIGNATURE PG OFFICE STAFF

REGISTERED

STAMP

.....

YES..... NO.....

An audit of genetic testing outcomes and sociodemographic factors of  
patients who received genetic counselling for hereditary breast cancer  
through the Division of Human Genetics

*Slindokuhle Sibiya*

2307784

MSc (Med) Genetic Counselling

Supervisor 1:

Monica Araujo

MSc (Med) Genetic Counselling, Genetic Counsellor, Lecturer, and Course Coordinator,  
Clinical and Counselling Unit, Division of Human Genetics, School of Pathology,  
Faculty of Health Sciences  
University of the Witwatersrand

Supervisor 2:

Elzette Gilfillan

MSc (Med) Genetic Counselling, Genetic Counsellor, Lecturer, and Course Coordinator,  
Clinical and Counselling Unit, Division of Human Genetics, School of Pathology,  
Faculty of Health Sciences  
University of the Witwatersrand

I **Slindokuhle Sibiya** (Student number: **2307784**) am a student registered for the degree of **MSc (Med) Genetic Counselling** in the academic year **2024**.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: SAS

Date: 24/07/2024

## **1. Background:**

### **1.1. Introduction**

Cancer constitutes a diverse group of more than 100 non-communicable diseases that develop over time, primarily due to the accrual of variants within an array of genes collectively recognised as oncogenes and tumour suppressor genes. These variants culminate in uncontrolled cell proliferation and the development of a cancer neoplasm. (Mitra *et al.*, 2018; National Institute of Health, 2007). The World Cancer Research Fund International (2022) reports cancer as one of the leading causes of death globally, with breast cancer being a significant contributor – accounting for 11.7% of cancer cases. Preventative strategies, including global population-level screening programs and more recently; family predictive testing have been implemented directed at mitigating this burden (Marteri *et al.*, 2022). However, despite the applied efforts, the global breast cancer burden continues to rise, especially in low to middle-income countries like South Africa – prompting the need to assess the current preventative, diagnostic, and treatment strategies, to identify caveats that can be improved upon.

### ***1.2. Molecular classifications: Hereditary breast cancer syndromes***

#### ***1.2.1. The aetiology of cancer***

Malignant neoplasms emerge primarily from genetic aberrations, therefore classifying cancer as a genetic condition. However, a substantial proportion of cancer incidences result from an intricate interplay among genetic, environmental, and behavioural determinants, therefore, classifying cancer as having a multifactorial aetiology (Vogt *et al.*, 1993). This multifaceted nature prompts a nuanced classification of cancer based on its causative factors, as either: sporadic/acquired, familial, or hereditary (Anderson, 1992). Despite being recognised as a genetic condition; hereditary cancers account for only 5-10% of cancer cases with the majority accounted for by sporadic cancer events (Sokolova *et al.*, 2023).

### 1.2.2. Hereditary breast cancer

Clinicians have subsequently identified defined traits that act as hallmarks of hereditary cancers, that allow them to distinguish hereditary cancer cases from other types to ensure appropriate management. These include an extensive family history, an early cancer onset, bilateral cancer occurrence, multiple affected family members, multiple cases of childhood cancers, and male breast cancers (Rahner & Steinke, 2008). These attributes are highly suggestive of the presence of a familial variant in genes associated with an increased predisposition to cancer development, as summarised in **Table 1**. Familial variants typically manifest in hereditary cancer syndromes, with the type dependent on the underlying affected gene

**Table 1: A summary of the common high- and moderate-risk cancer genes**

|               | Cancer-associated genes                           | Breast Cancer Risk (%) | Ovarian Cancer Risk (%) |
|---------------|---------------------------------------------------|------------------------|-------------------------|
| High-Risk     | <i>BRCA1, BRCA2, PTEN, PALB2, and TP53</i>        | 25 - 85                | 11 - 44                 |
| Moderate-Risk | <i>ATM, BRIP1, CHEK2, CDH1, STK11, and RAD51C</i> | 17 - 63                | 2 - 10                  |

(National Cancer Institute, 2024).

Of note are high-risk or founder populations that have particular variants that occur almost exclusively in those populations. These populations are marked by an increased incidence of a specific condition due to the presence of founder variants (Neuhasuen, 2000). South Africa has two high-risk breast cancer founder populations; the Afrikaner, and the Ashkenazi Jewish population, but some founder variants have been identified in other populations such as the Xhosa population. All groups present with *BRCA1* and *BRCA2* variants exclusive to the individuals of that population, posing a significantly higher risk of Hereditary Breast and Ovarian Cancer (HBOC) syndrome to individuals within these groups compared to the general South African population. (Seymour *et al.*, 2016; van der Merwe *et al.*, 2012).

### 1.2.3. Hereditary breast and ovarian cancer syndrome

Hereditary Breast and Ovarian Cancer (HBOC) syndrome, primarily linked to *BRCA1* and *BRCA2* variants, is a significant contributor to hereditary breast cancer incidence. While breast cancer is the primary concern, HBOC also increases the predisposition to ovarian cancer, evidenced by multiple cases in affected families (Darcy *et al.*, 2004). Occasionally, cases of melanoma, pancreatic, and prostate cancers are observed as part of the syndrome. Moreover, hereditary breast cancer can also arise in other cancer syndromes such as Lynch, Li-Fraumeni, Cowden, and Peutz-Jeghers due to variants in the *P53*, *PTEN*, and *STK11* genes respectively – with the breast cancer risk varying across the syndromes (Rich *et al.*, 2015). Beyond its genetic classifications, hereditary breast cancer can be characterised by histopathological features, evaluated through imaging and biochemical methods to assess tumour characteristics and hormone receptor status (Larsen *et al.*, 2014).

### ***1.3. Histopathological classifications of HBC***

#### ***1.3.1. Breast cancer molecular subtypes and histology***

Breast cancer tumours express key immunohistochemical markers that guide prognosis, prediction, and treatment selection. The oestrogen (ER), progesterone (PR), and the human epidermal growth factors 2 (HER2) receptors are vital among these markers. Contingent on these markers, breast cancers can be classified into four molecular subtypes based on their receptor status as shown in **Table 2** below.

***Table 2: The breast cancer molecular subtypes, and the corresponding receptor status***

| <b>Molecular subtype</b>     | <b>Corresponding receptor status</b> |        |        |
|------------------------------|--------------------------------------|--------|--------|
| Luminal A                    | ER +                                 | PR +   | HER2 - |
| Luminal B [HER2-]            | ER +                                 | PR -   | HER2 - |
| Luminal B [HER2+]            | ER +                                 | PR -/+ | HER2 + |
| HER2 – enriched              | ER -                                 | PR -   | HER2 + |
| Triple-negative / Basal-like | ER -                                 | PR -   | HER2 - |

(Kakudji *et al.*, 2021)

Moreover, breast cancer tumours are broadly categorized as either in situ or invasive carcinomas. In situ carcinomas involve abnormal cells confined to their original tissue layer without penetrating surrounding tissues, while invasive carcinomas infiltrate surrounding breast tissue. In situ types include ductal and lobular carcinomas, while invasive types include tubular, ductal, or lobular. These classifications depend on the site of the tumour and the specific breast cells affected. Ductal carcinomas, forming in milk duct linings, are most common, while a small proportion starts in breast lobules, known as lobular carcinomas (Lynch *et al.*, 1998; Sokolova *et al.*, 2023).

Histopathological variances distinguish hereditary from sporadic breast cancer tumours. Hereditary cases often exhibit adverse features, comprising high-grade tumours, negative

hormone receptor status, and elevated proliferation indices, indicating aggressive behaviour. These are hence, typically classified as invasive carcinomas (Arpino *et al.*, 2016). Tumours further vary based on underlying pathogenic variants; *BRCA1* and *PALB2* variants are linked to triple-negative, high-grade tumours, while *BRCA2*, *ATM*, and *CHEK2* variants are associated with a wider spectrum of tumour types, ranging from low to intermediate grade, classified as either luminal A or B (Angeli *et al.*, 2020). Identifying these subtypes aids in classification, and guides prognosis and treatment selection, thereby enhancing diagnostic accuracy.

#### ***1.4. Breast cancer diagnosis and management***

Globally, the current landscape for diagnosing and treating breast cancer prioritises genetic techniques over conventional methods like mammography, ultrasonography, and magnetic resonance imaging (Nounou *et al.*, 2015). While these traditional methods are still used complementarily, the shift towards a molecular-level understanding of breast cancer, which facilitates improved screening and early diagnosis has amplified the relevance of genetic techniques (Yang *et al.*, 2023). The current genetic testing landscape for breast cancer diagnostics is divided into two main aspects: investigations and management implementations. Investigations include predictive testing for asymptomatic individuals and risk assessment and diagnostic testing for symptomatic individuals, and management encompasses the subsequent prevention strategies, and targeted treatment regimens (Ahmed *et al.*, 2019).

##### ***1.4.1. Breast cancer risk prediction***

Before breast cancer diagnostic testing, risk assessment can estimate an individual's likelihood of carrying a breast cancer variant or developing the disease, aiding early detection and treatment stratification (Ahmed *et al.*, 2019). Factors like age, family history, and tumour pathology are considered. Assessment can be manual or software-based, with tools like CANRisk and the Manchester Scoring System (MSS) being utilised. CANRisk combines variant and cancer risk assessment, while MSS focuses on gene variant probability (Nelson *et al.*, 2019). These tools assist in determining genetic testing necessity, appropriate testing methods, and the likelihood of identifying pathogenic variants, greatly benefiting symptomatic patients.

##### ***1.4.2. Family predictive testing and prophylactic strategies***

Asymptomatic individuals can benefit from family predictive testing, outlined by Schwiter *et al.*, (2018), as the sequential testing of at-risk relatives for a genetic variant identified in a proband, aiming to identify those predisposed to breast cancer for early screening and intervention. This type of predictive testing targets asymptomatic individuals, based on the identification of a (likely) pathogenic variant in a cancer-associated gene, in a relative. Of

note: is the incomparable benefit observed in the performance of prophylactic surgeries like a salpingo-oophorectomy and a mastectomy, which have significantly reduced breast cancer occurrence in variant carriers identified through predictive testing (Ludwig et al., 2016).

Despite its benefits, global challenges in predictive testing implementation have prompted clinicians to develop strategies to improve uptake (Trevisan et al., 2023). Three principal strategies - direct, indirect, and assisted - are employed in predictive testing, each distinguished by how at-risk relatives are informed about their potential genetic risk (Schwiter et al., 2018). Genetic counsellors play a crucial role in facilitating family predictive testing, providing clear communication of genetic information and essential psychosocial support before and after testing, which significantly enhances uptake and allows early intervention and management (Srinivasan *et al.*, 2018).

#### *1.4.3. Management strategies and treatment plans*

Breast cancer management varies based on factors such as; a hereditary or sporadic nature, and impacting tumour biology aggressiveness. Treatments are classified as either local (surgery, and radiotherapy) for localised tumours, and systemic (chemotherapy, targeted therapy, and hormone therapy) for metastasised neoplasms (Hack *et al.*, 2015). Progression to a more molecular understanding of cancer, however, has led to the cancer molecular subtype presenting as the pre-eminent determinant of the treatment employed. Luminal A/B cancers respond well to hormone therapies and chemotherapy, HER-2 positive neoplasms require targeted therapy in addition to surgery and chemotherapy, and triple-negative breast cancers respond solely to chemotherapy (Sokolova *et al.*, 2023).

#### *1.5. The breast cancer diagnostic landscape in South Africa*

Breast cancer treatment in South Africa primarily occurs in specialised hospitals. While chemotherapy, surgery, radiotherapy, and hormone therapy are accessible in both private and state healthcare facilities, targeted therapy remains limited to private facilities (Dlamini *et al.*, 2023). Immense progress is evident in breast cancer surgery, which has in the past decade: notably progressed from an extremely under-resourced section to a well-developed sub-speciality. Screening programs have also shown improvement, emphasising self-examinations, clinical breast examinations, and mammography screening (Lince-Deroche *et al.*, 2017). Majority of patients in South Africa, however, often face barriers due to financial constraints, lack of awareness, and cultural influences that lead to the negligence of screening procedures (Dlamini *et al.*, 2023). Efforts to promote screening and family predictive testing are, however, underway as breast cancer is recognised as a national priority (Dlamini *et al.* 2023).

### ***1.7. Rationale***

Despite this declaration and the efforts exerted to mitigate the cancer burden, breast cancer incidence has witnessed a steady increase in the past decades (Dickens *et al.*, 2016). This increase can be accounted to several factors including: delayed diagnosis leading to later-stage diagnosis, limited healthcare access which furthers delayed diagnosis, and socioeconomic factors such as low levels of awareness and education and low income – which hinder ability to access preventative healthcare and early diagnosis. Furthermore, healthcare system challenges including insufficient resources and inadequate screening programs affect timely diagnosis and treatment, cultural beliefs and practices that influence health-seeking behaviors and lead to stigmas and misinformation around breast cancer also impact timely diagnosis, and urbanization and lifestyle changes in post-apartheid South Africa such as changes in diet and physical inactivity additionally contribute to an increased breast cancer risk. It is therefore imperative to thoroughly explore the multifaceted aspects that make up the current genetic testing landscape for breast cancer diagnostics, to identify factors contributing to the diminished efficacy of current healthcare systems, thus exacerbating the cancer burden. Clinical audits serve as an invaluable tool for establishing longitudinal data repositories, that are either procedure or condition-specific (Paton *et al.*, 2014). These repositories play a pivotal role in identifying areas needing improvement, thereby directing the implementation of education, research, and quality improvement strategies to improve patient care and outcomes. Retrospective audits, in particular, offer insights into historical benchmarks, to inform future research initiatives and improvement strategies (Esposito & Canton, 2014). This study therefore aims to review files of patients referred for genetic counselling for a personal and/or family history of breast cancer through the Division of Human Genetics from 2018 to 2024. The objective is to generate a REDCap database with information regarding the patient profiles and genetic testing landscape specific to breast cancer at the National Health Laboratory Services, Johannesburg, that can be used to uncover trends and relationships necessitating further investigation and research. Moreover, these databases will serve as valuable resources for future research endeavours within the division, particularly those focusing on hereditary breast cancer assessment.

## **2. Aim and study objectives:**

### **2.1. Aim:**

To conduct an audit of genetic testing outcomes and the associated sociodemographic factors of patients referred for genetic counselling for a personal and/or family history of breast cancer through the Division of Human Genetics from 2018 to 2024.

## ***2.2. Study objectives:***

1. To review patient files meeting the inclusion criteria, and record patient demographic data, family, personal and medical history, and genetic testing information onto a REDCap database.
2. To evaluate the uptake of diagnostic testing, and the results of patients who underwent genetic testing.
3. To evaluate the uptake of predictive testing in family members of patients with an identified pathogenic or likely-pathogenic variant in a gene associated with an increased risk of developing breast cancer.
4. To use statistical analyses to assess the association between patient factors and genetic testing outcomes to inform genetic testing approaches.

## **3. Study methodology:**

### **3.1. Study participants:**

Given that this study is a file review/audit, there will be no participant recruitment. All available files for patients seen after September 2018 for a hereditary breast cancer genetic consultation will be included in the study (data collection begins specifically in September of 2018 as this is when the REDCap database used for data collection in the study was implemented in the Division). For the prospective component, files will be collected for patients seen through the division for a hereditary breast cancer genetic consultation until June 2024. This includes patient records from the entire population of records available at the NHLS clinical and counselling unit for patients seen at the Charlotte Maxeke Johannesburg Academic Hospital breast cancer clinic, the Chris Hani Baragwanath Hospital breast cancer clinic, the Potchefstroom Hospital breast cancer clinic, the Helen Joseph Hospital breast cancer clinic, and the Wits Donald Gordon Medical Centre.

#### ***3.1.1. Inclusion criteria***

1. State and private patients:
  - a. Seen for a genetic consultation regarding a diagnosis, or risk of a hereditary breast cancer syndrome at NHLS clinical and counselling unit

any time between the September 2018 to the January 2024,

b. With files containing all essential data.

### *3.1.2. Exclusion criteria*

1. Patient files missing the essential data (as indicated in the data collection sheet) will also be excluded from the study population as missing or unreliable information can potentially hinder analysis and study outcomes.
2. Patients who present with a primary tumour other than breast cancer, even if they have a *BRCA1* or *BRCA2* variant.

Seeing as this is a file audit, which classifies it as an observational study where there is no manipulation/interference with the study participants: a control group is not required for this study; therefore, none is included. The sample size is anticipated to be ~1 000 individuals, based on the number of individuals seen for breast cancer in the unit between January 2018 to December 2023.

### **3.2. Study design:**

This study is a retrospective file review of hereditary breast cancer patient clinical records. The principle investigator will extract and record the relevant information from the patient records that meet the inclusion criteria. Selected records will be assessed and recorded into a predesigned datasheet for patient demographic data, personal, family, and medical history, and any other relevant information pertaining to the patient's breast cancer diagnosis and the investigations thereof (See Appendix One). Patient files will be accessed through the Division of Human Genetics Research Electronic Data Capture (REDCap) clinical database, by searching the database using keywords such as breast, triple-negative and *BRCA*.

### **3.3. Data analysis:**

After collecting the data, the relevant extracted information will be stratified into continuous and categorical data. The categorical data will be represented using graphs, pie charts, and percentages and/or frequencies. The continuous data will be added to the Statistica software program for quantitative data analysis. The preliminary step would be to determine whether the data is normally distributed. This will be done using the numerical Shapiro-Wilk test. If normality is detected, the data will be represented using mean, standard deviation and/or standard error. A Chi-squared test

will be employed to evaluate the association between specific categorical variables, a t-test will be utilised to explore potential relationships among continuous variables, and an ANOVA test will be used to assess the relationship between continuous and categorical data relevant to the study's objectives – such as those shown in Appendix Two. From the trends and relationships identified, a profile of genetic testing for hereditary breast cancer through the NHLS in the past six years can be constructed.

#### **4. Ethics**

Ethics approval is required for the study, to allow the use of patient data. Submission to the Human Research Ethics Committee (Medical) of the University of the Witwatersrand is scheduled in April 2024 – after which the study will commence. Patient data will be anonymised, with data reported making reference to the whole cohort and rarely to specific individuals. The researcher and the supervisors are the only individuals with access to the raw data.

#### **5. Timing**

|                      | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Literature Review    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Protocol preparation |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Protocol assessment  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Ethics application   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Data collection      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Data analysis        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Thesis write up      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Paper write up       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

#### **6. Funding**

Predicted budget:

| Activity                                                | Estimated Cost |
|---------------------------------------------------------|----------------|
| 1. Wits statistics workshops                            | R600           |
| 3. Wits data analysis workshop                          | R300           |
| 4. Internet access (for data analysis outside the NHLS) | R500           |
|                                                         | <b>R1 400</b>  |

## **7. Study limitations**

In line with the proposed study design, minimal limitations are anticipated in carrying out the project. The biggest identified challenge would be missing patient files/records and/or the lack of standardised information. This may result in the exclusion of some patients due to missing information. In light of the study methodology – which fully relies on the presence, collection, and analysis of patient records – this presents as a major challenge in completing the study. However, given the duration of patient records being analysed (6 years), it is justified to assume that ample patient records can be collected and identified for a powerful study and conclusive results. Furthermore, considering that the results of the study are relationships and trends inferred by the researcher through statistical analysis of the data obtained – the results may be subject to bias (formally known as systematic error; which is introduced when one outcome or answer is encouraged over others). However, this can be combatted by setting confidence intervals, which the statistical results have to fall within for a trend or relationship to be concluded and reported.

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## Appendix E: Turnitin Report and Plagiarism Declaration

### Final Clean Sub-1.pdf

#### ORIGINALITY REPORT

|                  |                  |              |                |
|------------------|------------------|--------------|----------------|
| <b>7</b> %       | <b>6</b> %       | <b>3</b> %   | <b>1</b> %     |
| SIMILARITY INDEX | INTERNET SOURCES | PUBLICATIONS | STUDENT PAPERS |

#### PRIMARY SOURCES

|          |                                                                                                                                                                                                                                       |                |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>1</b> | <b>www.ncbi.nlm.nih.gov</b><br>Internet Source                                                                                                                                                                                        | <b>1</b> %     |
| <b>2</b> | <b>Submitted to University of Witwatersrand</b><br>Student Paper                                                                                                                                                                      | <b>1</b> %     |
| <b>3</b> | <b>karger.com</b><br>Internet Source                                                                                                                                                                                                  | <b>1</b> %     |
| <b>4</b> | <b>discovery.ucl.ac.uk</b><br>Internet Source                                                                                                                                                                                         | <b>&lt;1</b> % |
| <b>5</b> | <b>Loureiro, Marta. "Prevalence of Pathogenic Variants in Breast Cancer Susceptibility Genes Among Patients with a Relatively Low Probability of Inherited Predisposition", Universidade do Porto (Portugal), 2024</b><br>Publication | <b>&lt;1</b> % |
| <b>6</b> | <b>Ruth Chadwick, John Dupré, David Wield, Steve Yearley et al. "Breast Cancer Gene Research and Medical Practices - Transnational perspectives in the time of BRCA", Routledge, 2014</b><br>Publication                              | <b>&lt;1</b> % |

|    |                                                                                                                                                                                                                                  |      |
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| 7  | wiredspace.wits.ac.za<br>Internet Source                                                                                                                                                                                         | <1 % |
| 8  | www.mdpi.com<br>Internet Source                                                                                                                                                                                                  | <1 % |
| 9  | https.ncbi.nlm.nih.gov<br>Internet Source                                                                                                                                                                                        | <1 % |
| 10 | Furu Wang, Qiaoqiao Fang, Zhen Ge, Ningle Yu, Sanxiao Xu, Xiangyong Fan. "Common BRCA1 and BRCA2 mutations in breast cancer families: a meta-analysis from systematic review", Molecular Biology Reports, 2011<br>Publication    | <1 % |
| 11 | www.cabrini.com.au<br>Internet Source                                                                                                                                                                                            | <1 % |
| 12 | www.science.gov<br>Internet Source                                                                                                                                                                                               | <1 % |
| 13 | T. Yanes, C. Wallingford, MA. Young, A.M. McInerney-Leo et al. "Development and evaluation of a novel educational program for providers on the use of polygenic risk scores", Cold Spring Harbor Laboratory, 2023<br>Publication | <1 % |
| 14 | link.springer.com<br>Internet Source                                                                                                                                                                                             | <1 % |
| 15 | docksci.com<br>Internet Source                                                                                                                                                                                                   | <1 % |

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| 16 | <a href="https://pubmed.ncbi.nlm.nih.gov">pubmed.ncbi.nlm.nih.gov</a><br>Internet Source                                                                                                        | <1 % |
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| 18 | Kiliç, Sabriye Senem. "Analysis of the Effect of Paclitaxel Induced Conditioned Media on Viability of Triple Negative Breast Cancer Cells.", Marmara Universitesi (Turkey), 2024<br>Publication | <1 % |
| 19 | <a href="http://www.sjsu-cs.org">www.sjsu-cs.org</a><br>Internet Source                                                                                                                         | <1 % |
| 20 | <a href="https://assets-eu.researchsquare.com">assets-eu.researchsquare.com</a><br>Internet Source                                                                                              | <1 % |
| 21 | <a href="http://ddd.uab.cat">ddd.uab.cat</a><br>Internet Source                                                                                                                                 | <1 % |
| 22 | <a href="http://samajournals.co.za">samajournals.co.za</a><br>Internet Source                                                                                                                   | <1 % |
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| 25 | Waldow, Grace. "Further Investigation of the First-Tier Status of Fragile X Testing for Pediatric Neurodevelopmental Disorders:                                                                 | <1 % |

## Diagnostic Yield and a Comprehensive Chart Review", University of Pittsburgh, 2024

Publication

26

"27th Annual The Charles A. Coltman, Jr. San Antonio Breast Cancer Symposium", Breast Cancer Research and Treatment, 2004

Publication

<1%

Exclude quotes Off

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## *Appendix F: Author Guidelines for South African Medical Journal*

### **Research articles**

*Guideline word limit: 4 000 words*

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

#### *Structured abstract*

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

[Here](#) is an example of a good abstract.

#### *Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.

- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

### Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the  $\pm$  symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

### Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

### Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

## Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
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- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

## Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
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